

# In-Hospital and 4-Year Clinical Outcomes Following Transcatheter Versus Surgical Closure for Secundum Atrial Septal Defect in Adults

## A National Cohort Propensity Score Analysis

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**Abstract:** Atrial septal defect (ASD) closure is major therapy for patients with secundum ASD. Although surgical closure (SC) and transcatheter closure (TC) are usually performed in such patients, data on the long-term outcomes comparing TC and SC in adults are limited.

Data on the participants of this cohort study were retrieved from Taiwan's National Health Insurance Research Database from 2004 to 2011. Secundum ASD patients > 18 years of age who underwent TC or SC were initially enrolled, and those with associated comorbidities were excluded. After propensity score matching, the clinical outcomes between the TC and SC groups were analyzed.

There were 595 patients recruited in the TC group and 308 patients in the SC group. The SC group had a higher incidence of systemic thromboembolism ( $P < 0.001$ ), ischemic stroke ( $P = 0.002$ ), and all-cause mortality ( $P = 0.013$ ) when compared with those of the TC group at the index hospitalization, and similar phenomena could also be seen in a around 4-year follow-up period after the procedures (systemic thromboembolism ( $P < 0.001$ , HR = 11.48, 95% CI: 3.29–40.05), ischemic stroke ( $P = 0.005$ , HR = 9.28, 95% CI: 1.94–44.39), and all-cause mortality ( $P = 0.035$ , HR = 2.28, 95% CI: 1.06–4.89). In addition, atrial fibrillation ( $P = 0.005$ ) and atrial flutter ( $P = 0.049$ ) more frequently developed in the SC group than in the TC group at the index hospitalization.

The adult secundum ASD patients had lower incidence rates of systemic thromboembolism, ischemic stroke, and all-cause mortality after TC than those after SC in the 4-year follow-up after procedures. Transcatheter ASD closure should therefore be given priority

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**Abbreviations:** AF = atrial fibrillation, ASD = atrial septal defect, AV = atrioventricular, NHIRD = National Health Insurance Research Database, PSM = propensity score method, SC = surgical closure, TC = transcatheter closure, TEE = transesophageal echocardiography.

## INTRODUCTION

Patients diagnosed with secundum atrial septal defects (ASDs) often have a benign prognosis, with a life expectancy elevated to an advanced age.<sup>1,2</sup> However, ASD patients have a higher risk of cardiovascular events, such as heart failure, stroke, and death<sup>3</sup> if they do not repair their ASD. More than half of these patients die before the age of 40 years.<sup>4</sup> The European Society of Cardiology (ESC) guidelines also recommend those patients with abnormally hemodynamic ASD receive ASD closure in order to reduce long-term complications.<sup>5</sup>

Among the techniques of ASD closure, surgical closure (SC) and transcatheter closure (TC) are usually performed. SC has been practiced for more than 5 decades and also leads to good long-term prognosis for ASD patients.<sup>3,6</sup> Patients with surgical ASD closure survive longer and the incidence of unfavorable cardiovascular events is also reduced.<sup>7</sup> TC as an alternative technique was first practiced in 1976.<sup>8</sup> With fewer postprocedure complications, lower risks of anesthesia and shorter hospital stay, TC is a relatively less invasive technique and has been widely used in recent years.<sup>9,10</sup> Several studies have thus compared SC and TC,<sup>11–13</sup> and although those studies revealed that patients after SC have higher incidences in complications of arrhythmia, pericardial effusion, and severe anemia and have longer length of hospital stay in short-term follow-up, there are still few reports on long-term data. There are also still inconsistent results in the previous studies<sup>11–15</sup> because of the limited number of well-matched or randomized clinical trials, and limited numbers of studies usually focus on the pediatric population.<sup>16</sup>

Therefore, in order to reduce influence of any confounding morbidity and bias, an adult population for study was retrieved from a Taiwanese nationwide dataset covering a period of 8 years (2004–2011). With a huge ASD population, a comparison of groups with well-matched baseline characteristics can be made. According to such a well-matched and restrictive design study, the long-term outcomes and the incidence of major cardiovascular complications at admission of ASD closure for both surgical and transcatheter ASD closure can be evaluated.

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## MATERIALS AND METHODS

### Data Source

This national cohort study was retrieved from the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institute. The NHIRD, which was established in 1995, enrolls up to 99% Taiwan's population (about 23.20 million in 2012) and the insurance reimburses all clinical managements and procedures, which include transcatheter ASD closure and surgical ASD closure. The NHIRD also records all the medical data from inpatient care to outpatient clinics and all the basic data of the beneficiaries such as age, sex, and underlying diseases as well as the hospital's characteristics. Previous studies have both described the NHIRD in detail<sup>17</sup> and validated the accuracy of its diagnostic data.<sup>18</sup>

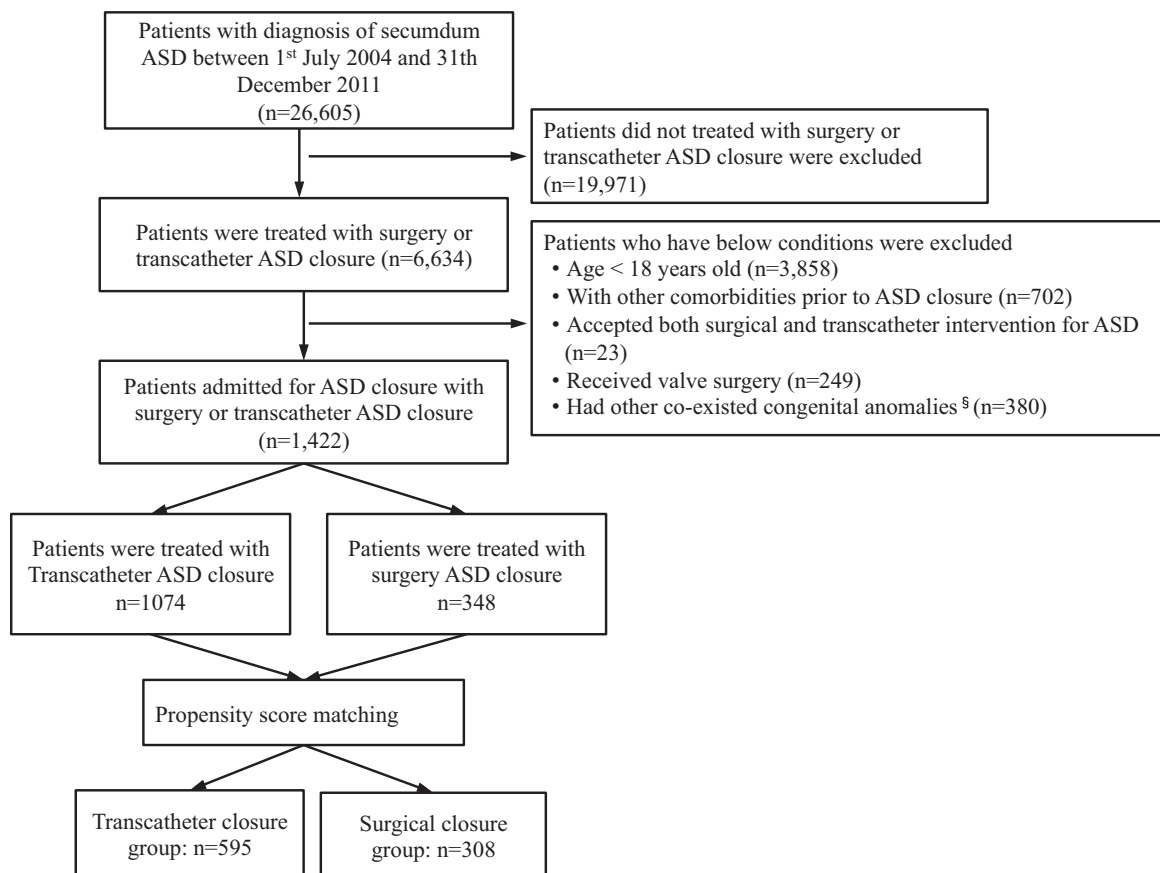
### Study Population

In the initial selection of the population set, there were 26,605 patients diagnosed with secundum ASD between January 1, 2004 and December 31, 2011. Several selection criteria were used. First, patients who accepted SC and TC, in accordance with the indication of ASD closure (pulmonary-systemic flow rate >1.5) in Taiwan National Insurance reimbursement, were enrolled. Second, patients under the age of 18 years were excluded. Third, patients were excluded if they had a

history of any cardiovascular events before closure procedures, baseline characteristics influencing the accuracy of confirmation of clinical outcomes and if they had received both surgical and transcatheter interventions. Fourth, in order to simply clarify the differences between TC and surgical ASD closures in clinical outcomes, we excluded patients who possibly needed a combination of other surgical procedures. Hence, patients with other coexisting congenital anomalies, significant valvular disorder, and who accepted valvular surgery were also excluded. Finally, a total of 1422 patients were identified and the enrollment of the study patients is shown in Fig. 1. In addition, all clinical comorbidities, complications, and outcomes were selected according to the International Classification of Diseases, Ninth Revision (ICD-9) (Supplemental Table 1, <http://links.lww.com/MD/A413>). Ethical approval was not necessary (as approved by The Institutional Review Board of Chang Gung Memorial Hospital: 102-1711B) because the data from the NHIRD consists of de-identified secondary data and is used for research purposes only.

### Transcatheter and Surgical ASD Closure Procedures

According to general clinical practice in Taiwan, transcatheter ASD closure was done under general anesthesia and intraprocedure trans-esophageal echocardiography (TEE) for



**FIGURE 1.** Flow-chart of study design. \*Other comorbidities included ischemic stroke, hemorrhage stroke, systemic thromboembolism, heart failure, high degree atrioventricular block, atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia. §Co-existing congenital anomalies: endocardial cushioning syndrome, Ebstein's anomaly, ventricular septal defect, ostium primum atrial septal defect, transposition of great vessels, and tetralogy of fallot.

guidance. The procedure was approached from femoral vein and the occluder was selected according to the estimated ASD diameter. The devices were implanted under fluoroscopic and TEE guidance according to the standard technique as reported in the literature.<sup>19</sup> The result was confirmed by intraprocedure TEE. SC of ASD was mostly through a median sternotomy, or submammary incision in case of secundum ASD.<sup>20</sup> Under general anesthesia, the cardiopulmonary bypass was set up and aortic cross-clamping and myocardial protection were delivered in usual manner. A standard right atriotomy was made and the anatomy of atrial septum was carefully checked under cardioplegic cardiac arrest. Either direct closure or pericardial patch reconstruction of the septal defect was chosen by the anatomy as well as surgeon's preference. The surgical result was confirmed immediately by intraoperative TEE before wean off the cardiopulmonary bypass.

**Study Design and Outcomes Assessments**

Minimizing the bias is more crucial than maximizing the precision when estimating the group differences (i.e., surgical vs transcatheter), especially in observation studies.<sup>21</sup> For this reason, we matched the surgical cohort with the transcatheter cohort by a 1:2 ratio using the propensity score method (PSM).<sup>22</sup> The covariates for calculating propensity score included age, gender, index year, and month, as well as underlying comorbidities, such as coronary artery disease, hypertension, diabetes, chronic obstructive pulmonary disease, liver cirrhosis, and chronic kidney disease. After PSM, the 2 cohorts were analyzed for the impacts of the 2 types of ASD intervention (i.e., transcatheter or surgical ASD closure) on clinical outcomes. Finally, 21 out of the 308 patients in SC group were matched with a corresponding counterpart, resulting in a total of 595 patients in the TC group. The outcomes were defined in terms of arrhythmias (high degree atrioventricular [AV] block, atrial fibrillation [AF], atrial flutter), systemic thromboembolic event, heart failure, and all-cause mortality. Systemic thromboembolism included ischemic stroke, acute myocardial infarction, cerebral embolism, transient cerebral ischemia, pulmonary embolism and infarction, arterial embolism, and thrombosis.

**Statistical Analysis**

The PSM matching algorithm was based on nearest-neighbor method (Greedy method) and used the caliper radius (set as 0.5 sigma), which signifies a tolerance level for the maximum distance in the propensity score. The covariates for the calculating propensity score are listed above in the study design section. The matching procedure was performed by using NCSS 2007 (Number Cruncher Statistical System, Limited Liability Company, Kaysville, UT).

The patents' clinical characteristics between the surgical and transcatheter ASD closures were compared using a *t*-test for continuous variables and Chi-square test or Fisher exact test for categorical variables whenever appropriate. The association between study groups and in-hospital complications were examined with multivariable logistic regression analysis. The event-free survival rates of long-term outcomes between the study groups were compared using a multivariable Cox proportional hazard analysis. Noticeably, the risk measure (i.e., odds ratio or hazard ratio) and its significance as well as confidence interval was not available when no event was developed in either study group. In such case, we reported Fisher exact test instead. All data analyses were conducted using IBM SPSS 22.0 (IBM SPSS Inc., Chicago, IL).

**RESULTS**

This cohort study consisted of 1422 adult secundum ASD patients, with a mean age of 40 ± 14.2 years, who accepted ASD closure. Female was predominant (1069/1422 (75.2%)) in this population. There were 1074 patients who accepted surgical ASD closure while 348 patients were treated with transcatheter ASD closure. The number of patients treated with SC decreased year by year, in contrast to the number of patients accepting TC (Fig. 2) The mean age of patients treated with SC was 41.5 ± 15.2 years, whereas the mean age of those undergoing TC was 39.9 ± 14.1 years (*P* < 0.01). The prevalence of coronary artery disease, hypertension, and diabetes was higher in the SC group than in the TC group, while the prevalence of chronic lung disease, liver cirrhosis, and chronic kidney disease was not significantly different between the two groups (Table 1). After PSM in a 2:1 ratio (TC group vs SC group), 595 patients comprised the TC group and 308 patients the SC group (Table 1). The mean follow-up period was around 4 years (3.9 ± 2.3 years in the TC group and 3.8 ± 2.4 years in the SC group).

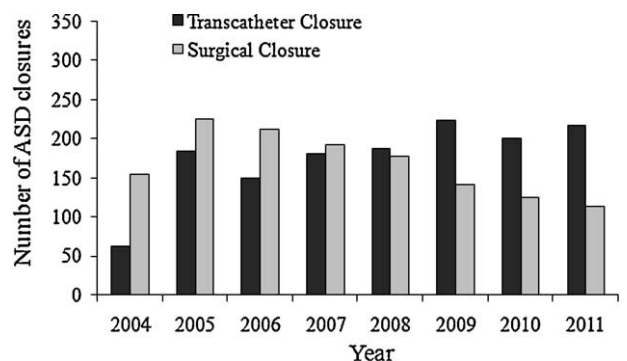
**In-Hospital Complications at the Index Hospitalization**

When comparing the 2 groups, the incidences of systemic thromboembolism (*P* < 0.001), ischemic stroke (*P* = 0.002), AF (odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.03–5.95, *P* = 0.043), and even in-hospital death (*P* = 0.013) were significantly higher in the SC group compared to the TC group. On the other hand, there were no significant differences in high degree AV block, atrial flutter, and heart failure (Table 2).

**Clinical Outcomes After Procedures**

Regarding the 4-year outcomes after discharge, there was no statistically significant difference between the 2 groups, except that there was a borderline higher incidence of AF in the TC group than in the SC group (1.7% vs 0%, *P* = 0.036). However, the incidence was rare and there were even no events in the SC group during the follow-up period (Table 3).

If the complications after the procedures are taken into consideration (combination with in-hospital complications and long-term outcomes after discharge), the SC group had higher incidences of systemic thromboembolism (HR: 11.48, 95% CI: 3.29–40.05, *P* < 0.001), ischemic stroke (HR: 9.28, 95% CI: 1.94–44.39, *P* = 0.005), and all-cause mortality (HR: 2.28, 95%



**FIGURE 2.** Absolute number of secundum atrial septal defect (ASD) closures (transcatheter closures and surgical closures) by year (2004–2011). Reintervention procedures are not included in this figure.

**TABLE 1.** Demographic and Clinical Data of the Study Patients Before and After PSM

Characteristics	Before PSM Matching			After PSM Matching (2:1)		
	TC Group	SC Group	P	TC Group	SC Group	P
Number of patients	1074	348	–	595	308	–
Age, y	39.9 ± 14.1	41.5 ± 15.2	0.065	40.0 ± 14.2	41.0 ± 14.8	0.352
Gender no., %			<0.001			0.934
Male	239 (22.3)	114 (32.8)		180 (30.3)	94 (30.5)	
Female	835 (77.7)	234 (67.2)		415 (69.7)	214 (69.5)	
Comorbidity no., %						
Coronary artery disease	27 (2.5)	29 (8.3)	<0.001	21 (3.5)	16 (5.2)	0.231
Hypertension	115 (10.7)	54 (15.5)	0.016	80 (13.4)	46 (14.9)	0.540
Diabetes	36 (3.4)	23 (6.6)	0.008	24 (4.0)	16 (5.2)	0.421
Chronic lung disease	11 (1.0)	7 (2.0)	0.152	5 (0.8)	4 (1.3)	0.511
Liver cirrhosis	3 (0.3)	1 (0.3)	0.980	1 (0.2)	0 (0.0)	0.472
Chronic kidney disease	3 (0.3)	2 (0.6)	0.419	1 (0.2)	2 (0.6)	0.233
Follow-up years y ± SD	3.4 ± 2.2	3.9 ± 2.5	<0.001	3.9 ± 2.3	3.8 ± 2.4	0.651

PSM = propensity score matching, SC = surgical closure, SD = standard deviation, TC = transcatheter closure.

CI: 1.06–4.89,  $P = 0.035$ ) than those in the TC group (Fig. 3 and Supplemental Table 2, <http://links.lww.com/MD/A413>). There were no significant differences in any arrhythmia events between the 2 groups (Supplemental Table 2, <http://links.lww.com/MD/A413>).

## DISCUSSION

This is a national-wide cohort study with a strict design for comparing the prognosis of SC with TC in adult hemodynamically significant secundum ASD patients. We created a similar distribution of baseline characteristics between the compared groups in order to reach the efficacy similar to that of a randomized clinical trial. In terms of outcomes in the follow-up period after procedure, when compared to the TC group, the SC group had an incidence of thromboembolic events that was 11.48 times greater, an incidence of ischemic stroke that was 9.28 times greater, and an incidence of all-cause mortality that was 2.28 times greater. For in-hospital complications, patients treated with SC experienced a high incidence

of systemic thromboembolism, ischemic stroke, and atrial arrhythmia. As for the 4-year clinical outcomes after discharge, the incidences of each outcome showed no significant differences between the 2 groups.

## Atrial Fibrillation and Atrioventricular Block

The reported incidence of atrial flutter and fibrillation in ASD patients only accepting medical therapy has been 15%–40% in patients between 35 and 40 years of age.<sup>4,23–26</sup> We observed that the incidences of new AF were 4.2% in patients accepting TC and 6.5% in those accepting SC (Table 2). Therefore, it is clear that intervention, regardless of method, can dramatically reduce the risk of new-onset AF.

As has been demonstrated in previous studies, preoperative AF and atrial flutter, and preoperative pulmonary hypertension are the independent risk factors for postoperative new-onset AF<sup>27,28</sup> in patients older than 40 years of age, and we also reduced the possible influencing factors by restrictively excluding criteria-excluding baseline characteristics of pulmonary

**TABLE 2.** The Association of Treatment With Complication at the Index of Hospitalization

New Onset Outcome	Number of Event, %		SC vs TC	
	TC Group (n = 595)	SC Group (n = 308)	OR (95% CI)	P
Systemic thromboembolism no., %	0 (0.0)	15 (4.9)	NA	<0.001*
Ischemic stroke	0 (0.0)	6 (1.9)	NA	0.002*
Arrhythmia no., %				
High degree AV block	3 (0.5)	0 (0.0)	NA	0.555*
Atrial fibrillation	10 (1.7)	16 (5.2)	2.47 (1.03–5.95)	0.043
Atrial flutter	1 (0.2)	4 (1.3)	8.11 (0.84–77.93)	0.070
Heart failure no., %	27 (4.5)	22 (7.1)	1.68 (0.91–3.12)	0.098
In hospital death no., %	0 (0.0)	4 (1.3)	NA	0.013*

Adjusted for age, gender, coronary artery disease, hypertension, diabetes, chronic lung disease, liver cirrhosis, and chronic kidney disease. AV = atrioventricular block, CI = confidence interval, NA = not applicable due to no event being observed in either group, OR = odds ratio, SC = surgical closure, TC = transcatheter closure.

\* Fisher exact test.

**TABLE 3.** Four-Year Clinical Outcomes After Discharge

Outcome of Time to Event	N*	Number of Event, %		SC vs TC	
		TC Group	SC Group	HR (95% CI)	P
Systemic thromboembolism no., %	885	3 (0.5)	4 (1.4)	2.66 (0.55–12.88)	0.225
Ischemic stroke	894	2 (0.3)	3 (1.0)	5.08 (0.75–34.33)	0.095
Arrhythmia no., %					
High degree AV block	896	0 (0.0)	0 (0.0)	NA	NA
Atrial fibrillation	873	10 (1.7)	0 (0.0)	NA	0.036†
Atrial flutter	894	4 (0.7)	0 (0.0)	NA	0.306†
Heart failure no., %	851	5 (0.9)	4 (1.4)	1.06 (0.22–5.20)	0.940
Mortality after discharge no., %	899	15 (2.5)	13 (4.3)	1.80 (0.78–4.11)	0.166

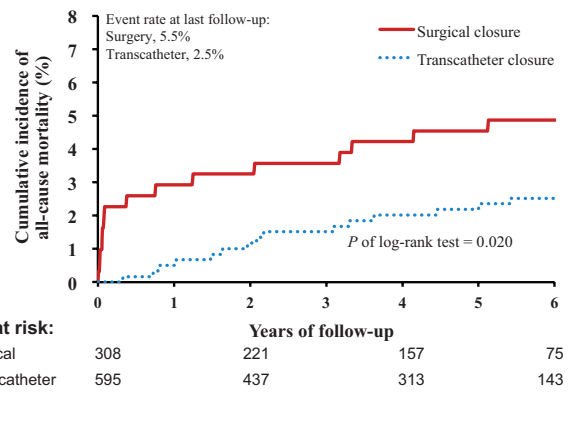
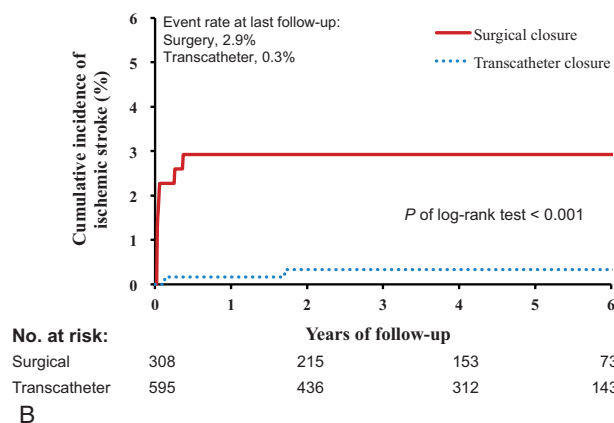
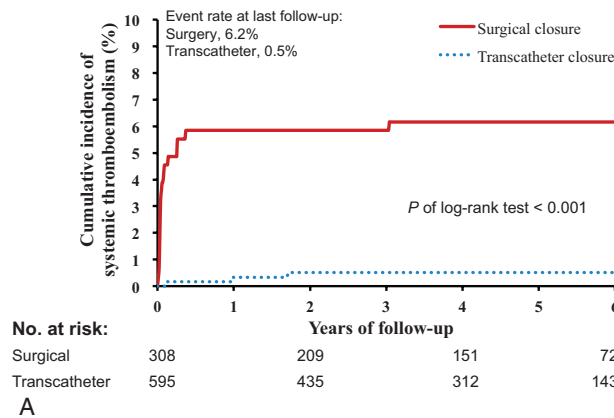
Adjusted for age, gender, coronary artery disease, hypertension, diabetes, chronic lung disease, liver cirrhosis, and chronic kidney disease. AV = atrioventricular block, CI = confidence interval, NA = not applicable due to no event being observed in either group, OR = odds ratio, SC = surgical closure, TC = transcatheter closure.

\* Excluding those occurring or dying at the index hospitalization.

† Fisher exact test.

hypertension, AF, and atrial flutter. Comparing the TC and SC groups, our data show that patients undergoing TC had a lower occurrence rate of AF than those undergoing SC in postoperation hospitalization. However, there was no significant difference for long-term follow-up period. Moreover, there were no

differences in incidence of high degree AV block between the TC and SC groups. Therefore, we conclude that surgical intervention will affect the new onset of AF in the perioperation period but not affect the long-term incidence after discharge, when compared with transcatheter intervention.



**FIGURE 3.** Cumulative incidence of outcomes during the follow-up period: (A) shows the cumulative incidence of thromboembolic event in transcatheter closure group and surgical closure group; (B) shows the cumulative incidence of ischemic stroke in transcatheter closure group and surgical closure group and (C) shows the cumulative incidence of all-cause mortality in transcatheter closure group and surgical closure group.



## Stroke and Thromboembolism

The prevalence of stroke in open ASD is reported to be 4% in patients of a mean age of 36.4 years.<sup>29</sup> We found a lower incident rate of 0.3% in the TC group and 2.9% in the SC group, which indicates that both methods might prevent ischemic stroke, although several studies showed no significant difference in stroke between 2 groups.<sup>10,14</sup> We noted that the incidences of ischemic stroke and systemic thromboembolism were higher in the SC group than in the TC group at the index hospitalization. Again, the difference might be attributed to the surgical effect such as hemodynamic changes during general anesthesia and emboli formation during surgery closure.

## Mortality and Heart Failure

In the literature, long-term mortality in ASD patients under closure intervention ranges from 3 to 5%<sup>10,14,15,23</sup> and short-term mortality is from 0% to 1.2%, and even no perioperative death occurring among patients with surgical repair.<sup>25,27,30,31</sup> Our results accorded with these findings. When comparing surgical and TC in ASD patients, some studies have shown no significant differences in short-term and long-term survival rates.<sup>10–15</sup> Our study, however, showed that the patients receiving TC had a lower all-cause mortality than those receiving SC. When we further conducted a subgroup analysis of in-hospital complications and the long-term outcome after discharge, a difference between the 2 groups was found for in-hospital mortality but there was no difference in long-term mortality after discharge between the 2 groups. Furthermore, since surgical ASD closure is a more invasive technique with higher risk of analgesia, wound infection, and other perioperative complications,<sup>9,10</sup> the perioperative mortality rate could be partially affected by the surgical intervention. Thus, the better perioperative outcome in the TC group was found in our report, and the difference of all-cause mortality between the 2 groups might be attributed to the surgical effect, just as it did for the incidences of ischemic stroke and systemic thromboembolism. As for heart failure after ASD closure, some studies have suggested that the development of acute heart failure is due to the abrupt elevation in the left ventricular preload following ASD closure.<sup>32</sup> This study did not find any significantly different effect on the heart failure between the TC and SC procedures.

## LIMITATIONS

This retrospective analysis bears the limitations typical of this kind of study. First, one major limitation was the accuracy of diagnosis. Potential misdiagnosis exists in the NHIRD due to the possible misclassification of codes. By adjusting for this bias, we retrieved patients from not only the diagnostic code, but also the procedure code as well for further confirmation. Another limitation was that we could not evaluate the severity of ASD among the patients due to the absence of both detailed results from any examination and clinical presentations in the NHIRD database. Hence, we set a strict design to make a population with simple and similar baseline characteristics. We assumed that there might be no severe ASD patients in our study, who usually die or who undergo intervention at a young age.<sup>3,4</sup> In addition, because several comorbidities always play a significant role in the severity of heart condition in adult ASD patients,<sup>33</sup> propensity score matching was used for advanced participant-selection to ensure no significant disparity in follow-up time and baseline characteristics between surgical or transcatheter intervention. Furthermore, we excluded any

patient accepted combined SC of ASD with other cardiac surgery, such as valve replacement/revision to prevent more complicity of ASD structure in SC group than those in TC group. Second, the study cannot show any incidences of occluder migration/embolization and device erosion during/after TC because there is no periprocedure condition as well as details during surgical procedures in the NHIRD. Therefore, we tried to exclude as many such patients as possible by excluding those needing another surgery for ASD. Furthermore, to our knowledge, no study has ever mentioned the correction between device erosion, device migration/embolism, and the risk of mortality/morbidities.

## CONCLUSION

The incidences of all-cause mortality, AF, and ischemic stroke in patients after ASD closure, regardless of interventional methods, were found to be lower than those in patients following the natural course of ASD. In the long-term follow-up, patients accepting TC had better outcomes in all-cause mortality, and the development of ischemic stroke and systemic thromboembolism than those accepting SC. Moreover, patients treated with TC had a lower occurrence rate for the new onset of AF at admission than those treated with SC. These noteworthy and reliable findings suggest that a higher priority for the ASD closure should be given to TC rather than SC in the majority of hemodynamically significant adult secundum ASD patients.

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